PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

Appellants	:	Julie K. Bush, *et al.*	
Serial No.	:	10/520,360	
International Filing Date	:	July 8, 2003	Group Art Unit: 1612
US National Entry	:	January 5, 2005	
For	:	CRYSTALLINE 2,5-DIONE-3-(1-METHYL-1H-INDOL-3-YL)-4-[1-PYRIDIN-2-YLMETHYL)PIPERIDIN-4-YL]-1H-INDOL-3-YL]-1H-PYRROLE MONO-HYDROCHLORIDE	Examiner: Sabiha Naim Qazi
			Conf. No.: 5540
Docket No.	:	X-14884	

APPEAL BRIEF (37 C.F.R. § 41.37) FOR JULIE KAY BUSH, et al.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on July 29, 2008.

Appellants appeal from the Final Rejection of Claim 2 and its dependent Claim 15 in the present application under 35 U.S.C. §102(b), 35 U.S.C. §102(e), and 35 U.S.C. §103(a) dated April 30, 2008.

The fees required under §41.20 are dealt in the accompanying FEE TRANSMITTAL sheet.

REAL PARTY IN INTEREST

The Real Party in Interest of the present case is Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, 46285, as the inventors of the subject matter in the

above-referenced application assigned in August 2002 all inventions disclosed in the above-referenced application to Eli Lilly and Company.

RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claim 2 and its dependent Claim 15 are currently pending. Claims 1, 3-14, and 16-22 were previously cancelled. In the Office Action dated April 30, 2008, Claim 2 and its dependent Claim 15 were finally rejected under 35 U.S.C. §102(b), 35 U.S.C. §102(e), and 35 U.S.C. §103(a) and it is this final rejection of Claim 2 and its dependent Claim 15 under 35 U.S.C. §102(b), 35 U.S.C. §102(e), and 35 U.S.C. §103(a) that is being appealed.

STATUS OF AMENDMENTS

No amendments have been submitted subsequent to Final Rejection in the present case.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellant's invention relates to a particular crystalline mono-hydrochloride form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole having an X-ray diffraction pattern comprising the following peaks: 6.8 ± 0.1, 10.9 ± 0.1, 14.2 ± 0.1 and $16.6 \pm 0.1°$ in 2θ; when the pattern is obtained from a copper radiation source (CuKα; $\lambda = 1.54056$ Å). (see specification on page 3, lines 6-11; Figure 1; page 5, lines 27-31; page 6-page 10; and Example 1 on page 14) and pharmaceutical compositions comprising the same.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 2 and 15, which relate to a particular crystalline mono-hydrochloride form of 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole having a specific X-ray diffraction pattern, were properly rejected under 35 U.S.C. §102(b) as being anticipated by WO 02/02094 A2 (hereinafter referred to as "TEICHER") and US 5,545,636 (hereinafter referred to as "HEATH"), which teach the freebase (hereinafter referred to as "FB") and a poorly crystalline di-hydrochloride form of 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole.

2. Whether Claims 2 and 15, which relate to a particular crystalline mono-hydrochloride form of 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole having a specific X-ray diffraction pattern, were properly rejection under 35 U.S.C. §102(e) as being anticipated by HEATH.

3. Whether Claims 2 and 15, which relate to a particular crystalline mono-hydrochloride form of 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole having a specific X-ray diffraction pattern, were properly rejected under 35 U.S.C. §103(a) as being obvious over TEICHER and HEATH, which teach the FB and a poorly crystalline di-hydrochloride forms of 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole.

ARGUMENT

35 USC §102(b)—1st Rejection

Claim 2 and its dependent Claim 15 were improperly rejected under 35 U.S.C. §102(b) as being anticipated by TEICHER.

A reference can only anticipate a claim if "each and every limitation is found either expressly or inherently in [that] single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998). Thus, the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently. *Glaxo Inc. v. Novopharm* Ltd., 52 F.3d 1043, 1047 (Fed. Cir. 1995).

The present claimed invention is "Crystalline 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole mono-hydrochloride having an X-ray diffraction pattern which comprises the following peaks: 6.8 ± 0.1, 10.9 ± 0.1, 14.2 ± 0.1 and 16.6 ± 0.1° in 2θ; when the pattern is obtained from a copper radiation source (CuKα; λ = 1.54056 Å)." This therefore requires the following elements:

1. the compound;
2. a salt of the compound;
3. the mono-hydrochloride salt of the compound;
4. that it is crystalline; and
5. that the particular crystalline form be characterized by the XRD data shown above.

The Examiner relies on five sections of TEICHER to support an assertion of anticipation:

1. TEICHER lines 1-10, p. 7: "a compound of Formula 1 or a pharmaceutically acceptable salt or solvate thereof," relating generally to salts and solvates of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole through recitation of "a pharmaceutically acceptable salt or solvate thereof."

2. Claims 1, 3-7 and 13 of TEICHER: relating generally to salts and solvates of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole by recitation of "a pharmaceutically acceptable salt or solvate thereof."

3. TEICHER lines 13-32, p. 8: listing acid addition salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole and stating a preference for hydrochloride salts:

> "Because it contains a basic moiety, the compound of Formula 1 can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include such inorganic acids as hydrochloric….Particularly the hydrochloric and mesylate salts are used."

4. TEICHER lines 27-31, p. 11 and TEICHER lines 20-30, p. 14: describing use of a specific di-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole:

> "The following examples are provided merely to further illustrate the present invention….In each of the following examples, the compound of Formula 1 is administered as the dihydrochloride salt, and the amounts administered are given in terms [sic] amounts of the dihydrochloride salt."
>
> "The human SW2 small cell lung carcinoma xenograft was grown subcutaneously in male nude mice and the compound was administered to the animals along with cytotoxic chemotherapy in the sequential treatment regimen. The tumor growth delay produced by administration of 30mg/kg of the compound 317615.2HCl on days 14 through 30 to animals bearing the SW2 tumor was 10 days…."

5. TEICHER lines 1-5, p. 9: relating specifically to solvate salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole and their possible source (it should be noted that while the term "solvate" was originally recited in Claim 2, it was excised by subsequent amendment):

> "The pharmaceutically acceptable salts of the compound of Formula 1 can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent."

Based on the foregoing evidence, the Examiner concluded:

> "In claim 2 the Applicant has cited X-ray diffractions of their crystalline compound. However, since TEICHER *et al* discloses the crystalline forms of this compound and since the compound of prior art exists in crystalline form has the same utility and since no distinction has been made, claim 2 is considered anticipated by the prior art….."

(Final Rejection dated 04/30/08, p. 4, third paragraph). The Examiner further asserted that "since there is no showing, teaching or comparative data that the prior art hydrochloride is not the same as presently claimed, the claims of the present invention are anticipated by the reference." (Final Rejection dated 04/30/08, p. 4, final paragraph). Applicants respectfully assert that the rationale and conclusions reached by the Examiner are erroneous for the following reasons.

First, the foregoing passages from TEICHER generically disclose pharmaceutically acceptable salts or solvates of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-

ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, prefers hydrochloric salts, exemplifies one specific, crystalline form of the di-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, and suggests, at most, that solvate salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole could potentially be crystalline.

Second, TEICHER merely discloses a genus of pharmaceutically acceptable salts or solvates, of which hydrochloride salts can be a member, along with a di-hydrochloride species. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

Third, TEICHER does not even teach a mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, which is distinguished from mono-hydrochloride form by stoichiometry alone. More particularly, TEICHER does not teach a crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, and even more particularly, TEICHER does not teach the specific crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole claimed by Appellants with the specific XRD pattern claimed by Appellants, much less how to make it. In fact, there is no teaching that hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole are generally crystalline, rather than amorphous. Thus, the Examiner has not met the burden of finding "each and every limitation" of a claim as necessary to prove anticipation.

Further, Appellants are perplexed by the Examiner's request for comparative data to overcome the 102 rejections. Comparative data is generally used to rebut an assertion of *prima facie* obviousness; it is irrelevant to an anticipation analysis, unless a rejection is made under 37 CFR 1.105. Again, the level of skill of persons in the art is well known. The prior art clearly teaches that the HCl salt is present as a 2:1 acid:free base ratio. The present invention clearly describes that it is a 1:1 stoichiometry. Having the Applicants describe the well-known techniques to determine this is superfluous. The Examiner has the information necessary to determine the novelty of the present invention. There is nothing more that is needed.

Nevertheless, Appellants claim a new crystalline form of a previously unknown salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-

3-yl]-1H-pyrrole with different properties than the di-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole exemplified in TEICHER, as discussed on page 2, lines 8-22 of the specification:

> "The dihydrochloric acid salt of the FB is hygroscopic, whereas the mono-hydrochloride salt of the FB is not significantly hygroscopic. In addition, although the dihydrochloric acid salt of the FB appears to be crystalline by optical light microscopy, more detailed study by X-ray powder diffraction (XRD) has revealed that this material is in fact only poorly crystalline."

> "Surprisingly, in accordance with the invention, it has now been discovered that the mono-hydrochloride salt of FB is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state."

Moreover, the specification provides comparison data distinguishing the claimed mono-hydrochloride crystalline form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole over a crystalline form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole (specification p. 8, line 14 to p. 10, line 25)

Therefore, based on the limitations discussed supra, the Examiner has demonstrated the prior art teaches the compound (1) and some salts thereof (2). The Examiner has not shown how the prior art teaches: the mono-hydrochloride salt of the compound (3); that said mono-hydrochloride salt is crystalline (4) or that said crystalline mono-hydrochloride salt has the relevant XRD pattern (5).

In view of the foregoing remarks, Appellants respectfully assert that the final rejection of Claims 2 and 15 under 35 U.S.C. §102(b) as being anticipated by TEICHER was improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §102(b) —2nd Rejection

Claim 2 and its dependent Claim 15 were improperly rejected under 35 U.S.C. §102(b) as being anticipated by HEATH.

The Examiner relies on five sections of HEATH to support an assertion of anticipation:

1. Example 49 in Col. 45 and 46 of HEATH: disclosing "the free base compound of formula FB.

2. Examples 45 and 46 in col. 43 and 44 of HEATH: relating to specific derivatives of FB in crystalline forms.

3. Formulas II and III in col. 3 and 4 of HEATH: relating to a genus of compounds and "pharmaceutically acceptable salts or solvates thereof.

4. A list of acid addition salts of the compounds of Formulas II, III and IV in Col. 3 and 4, including hydrochloric salts.

5. "Examples, abstract and claims" without pointing out with specificity how these sections anticipate Claims 2 and 15.

Finally, the Examiner asserts that "since there is no showing, teaching or comparative data that the prior art hydrochloride is not the same as presently claimed, the claims of the present invention are anticipated by the reference." (Final Rejection dated 04/30/08, p. 4, final paragraph). Applicants respectfully assert that the rationale and conclusions reached by the Examiner are erroneous for the following reasons.

First, the foregoing passages from HEATH teach (1) teach a genus of compounds containing 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole or "a salt or solvate thereof" (including hydrochloric salts); (2) exemplify one form of FB; and (3) suggest that certain derivatives of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole can exist in crystalline form.

Second, HEATH has merely disclosed a genus of pharmaceutically acceptable salts or solvates of which hydrochloride salts can be a member. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

Third, HEATH does not teach mono-hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, more particularly, crystalline mono-hydrochloride salts thereof, and even more particularly, the specific crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole claimed by Appellants with the specific XRD pattern claimed by Appellants or how to make it. In fact, there is no teaching that hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole are generally crystalline, rather than amorphous. Thus, it can hardly be said that the Examiner has met her burden of finding "each and every limitation" necessary to prove anticipation.

Further, just as discussed with the anticipation rejection over TEICHER, Applicants submit there is no need to provide comparative data.

Moreover, the specification provides comparison data distinguishing the claimed mono-hydrochloride crystalline form of the compound over a crystalline form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole (specification p. 8, line 14 to p. 10, line 25)

In view of the foregoing arguments, Appellants respectfully assert that the final rejection of Claims 2 and 15 under 35 U.S.C. §102(b) as being anticipated by HEATH was improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

Rejection under 35 USC §102(e)

Claim 2 and its dependent Claim15 were improperly finally rejected under 35 USC §102(e) as being anticipated by HEATH on the same grounds as for the 35 USC §102(b) rejection discussed above.

35 USC §102(e) states (A person shall be entitled to a patent unless)::

> the invention was described in - (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

As such, the same remarks and arguments asserted by Appellants in the above section addressing the 35 USC §102(b) rejection under HEATH apply equally to the present rejection because the invention of the mono-hydrochloride was not described by HEATH or anyone else prior to Appellants' application date.

HEATH has merely disclosed a genus of pharmaceutically acceptable salts or solvates of which hydrochloride salts can be a member. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

HEATH does not teach mono-hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, more particularly, crystalline mono-hydrochloride salts thereof, and even more particularly, the specific crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole claimed by Appellants with the specific

XRD pattern claimed by Appellants or how to make it. In fact, there is no teaching that hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole are generally crystalline, rather than amorphous. Thus, it can hardly be said that the Examiner has met her burden of finding "each and every limitation" necessary to prove anticipation.

Further, just as discussed with the anticipation rejection over TEICHER, Applicants submit there is no need to provide comparative data.

In view of the foregoing arguments, Appellants respectfully assert that the final rejection of Claims 2 and 15 under 35 U.S.C. §102(e) as being anticipated by HEATH was improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §103(a)—1st Rejection

Claims 2 and 15 were improperly rejected under 35 USC §103(a) as being obvious over TEICHER. This conclusion of *prima facie* obviousness is clearly erroneous because the Examiner has failed to follow the proper test for obviousness determinations in cases of polymorphs laid out by *In re Cofer*, 148 USPQ 268 (CCPA 1966): i.e., whether the prior art would suggest: (a) the existence of another form of the molecule; (b) the structure of that form; and (c) a means of making it.

> "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the 'subject matter as a whole' to be compared with the prior art as are other properties of the material which make it useful."

Id. at 270 (emphasis added). This test was more recently also followed in *Ex parte Gala and Dibenedetto*, Appeal No. 2001-0987, US Patent 6,335,347, (Bd. Pat. App. & Int. June 28, 2001) (unpublished). In fact, the *Cofer/Gala* test is still consistent with *Graham* v. *John Deere Co. of Kansas City*, 383 U. S. 1 (1966), as it was re-emphasized by *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007). In *Graham*, The Supreme Court set out an objective analysis for applying §103 by determining: 1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any secondary considerations. In this way, the courts have been consistent in treating polymorphs as they would any other invention.

The Examiner relies on six sections of TEICHER to support an assertion of obviousness:

1. Lines 6-10, p. 9: "The compound of Formula I is used in combination with conventional anti-neoplasm therapies to treat mammals, especially humans, with

neoplasia. The procedure for conventional anti-neoplasm therapies, including chemotherapies using anti-neoplastic agents and therapeutic radiation, are readily available, and routinely practiced in the art, e.g., see Harrison's PRINCIPLES OF INTERNAL MEDICINE 11th edition, McGraw-Hill Book /Company."

2. Claims 1, 3-7, and 13: relating generally to salts and solvates of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole by recitation of "a pharmaceutically acceptable salt or solvate thereof."

3. Lines 1-10, p. 7: "a compound of Formula 1 or a pharmaceutically acceptable salt or solvate thereof," relating generally to salts and solvates of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole through recitation of "a pharmaceutically acceptable salt or solvate thereof."

4. Lines 13-32, p.8: "Because it contains a basic moiety, the compound of Formula 1 can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include such inorganic acids as hydrochloric….Particularly the hydrochloric and mesylate salts are used."

5. Lines 27-31, p. 11: "The following examples are provided merely to further illustrate the present invention….In each of the following examples, the compound of Formula 1 is administered as the dihydrochloride salt, and the amounts administered are given in terms [sic] amounts of the dihydrochloride salt."

6. Lines 1-2, p.9: "The pharmaceutically acceptable salts of the compound of Formula 1 can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent."

Appellants respectfully assert the foregoing passages of TEICHER do not teach or suggest: (a) the existence of the mono-hydrochloride; (b) the structure of the mono-hydrochloride; and (c) a means of making it as required by *In re Cofer*. Furthermore, when the Graham factors are weighed, a crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole cannot be obvious.

First, the scope and content of TEICHER merely discloses a genus of pharmaceutically acceptable salts or solvates of which hydrochloride salts can be a member, along with a di-hydrochloride species. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

Second, TEICHER is different from the present invention in that it does not teach or suggest a mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, which is distinguished from a di-hydrochloride salt by stoichiometry alone. More particularly, TEICHER does not teach or suggest a crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, and even more particularly, TEICHER does not teach or suggest the specific crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole claimed by Appellants having the specific XRD pattern claimed by Appellants, much less how to make it. In fact, there is no teaching that hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole are generally crystalline, rather than amorphous, and the only crystalline material taught in TEICHER is one Example of the di-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole. The art should teach or suggest every limitation of the claim, either explicitly or inherently.

Third, Appellants note that the passage relating specifically to "solvate salts", lines 1-2, page 9 is referring to solvate salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, not anhydrous salt forms. In fact, although the term "solvate" was originally recited in Claim 2, it was excised by subsequent amendment because the Examiner objected that the recited X-ray diffraction pattern could not apply to both the anhydrous and solvate forms of the claimed crystalline material. This passage only provides a possible source of any solvate salts that might form; it makes no assertion as to their probability of formation. Such formation can only be implied.

Fourth, one of ordinary skill in the art would not have been motivated to seek a new form of the 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole because, as noted on p. 2, lines 15-18 of the specification, Appellants were the first to discover that the di-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole was poorly crystalline and hygroscopic. Under these facts, a general motivation to prepare other selective PKC inhibitor compounds (i.e., derivatives of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole rather than new forms thereof) is insufficient.

Fifth, no rationale is presented as to how one of ordinary skill would predict and prepare the particular crystalline form of the mono-hydrochloride salt of the compound by

Appellants as is required by the third prong of the *In re Cofer* test. In fact, the first procedure for preparing the claimed crystalline material was described in the present specification. (specification p. 14, lines 1-33) The rationale of *In re Heoksema* is applicable here:

> "If the prior art of record fails to disclose or render obvious a method of making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compound overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds."

(399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968)). This rationale is still appropriate after KSR.

Sixth, in addition to ignoring the test of *In re Cofer*, the Examiner fails to take into account the unpredictability of the crystallization art, such that the structure of any allegedly obvious new form, or its associated properties, cannot be determined by theory. Acid-base reactions (i.e., to form acid addition salts) are predictable in solution based on the relative pKas of the reactants. However, the resulting salts are generally amorphous, and there is no reliable predictor of crystallization. Compare this to *Pfizer v. Apotex*, 82 USPQ2d 1321 (Fed. Cir. 2007), wherein the formation of a new salt was considered obvious under *KSR*, whereas the present invention requires that the salt be crystalline with a particular XRD pattern, which cannot be predicted from the art.

Based on the foregoing arguments, claims 2 and 15 cannot be *prima facie* obvious over TEICHER, so that comparative data for rebuttal cannot be required.

In view of the foregoing arguments, Appellants respectfully assert that the final rejection of Claims 2 and15 under 35 U.S.C. §103(a) as being obvious over TEICHER was improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §103(a)—2nd Rejection

Claims 2 and Claim 15 were improperly rejected under 35 USC §103(a) as being obvious over HEATH.

The Examiner relies on five sections of HEATH to support an assertion of obviousness:

1. Example 49 in Col. 45 and 46: (FB)

2. Formulas II and III in col. 3 and 4: (i.e., genus of compounds and "pharmaceutically acceptable salts or solvates thereof."

3. Abstract (i.e., genus of compounds); Claims (i.e., genus of compounds including 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole and a "salt of solvate thereof."); and Examples (i.e., 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole and derivatives thereof)

4. Formulas II, III and IV in Col. 3 and 4: including hydrochloric salts thereof (cited in 102(b) rejection but apparently overlooked here)

5. Examples 45 and 46 in col. 43 and 44 (i.e., crystalline derivatives of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole) specifically, and by the Examples.

Appellants respectfully assert the foregoing passages of HEATH do not teach or suggest: (a) the existence of the mono-hydrochloride; (b) the structure of the mono-hydrochloride; and (c) a means of making it as required by *In re Cofer*.

First, the scope and content of the passages of HEATH that the Examiner has cited merely disclose a genus of pharmaceutically acceptable salts or solvates of which hydrochloride salts can be a member. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

Second, HEATH is different from the present invention in that HEATH does not teach or suggest a mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole. More particularly, HEATH does not teach or suggest a crystalline mono-hydrochloride salt of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole, and even more particularly, HEATH does not teach or suggest the specific crystalline mono-hydrochloride salt of the compound by Appellants with the specific XRD pattern claimed by Appellants, much less how to make it. In fact, there is no teaching that hydrochloride salts of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole are generally crystalline, rather than amorphous. The only crystalline materials taught in HEATH are some Examples demonstrating that some derivatives of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole can exist in crystalline forms.

Third, one of ordinary skill in the art would not have been motivated to seek a new form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole because, as noted on p. 2, lines 8-10 of the specification, Appellants were the first to discover that preparation of the prior art form resulted in the unpredictable

formation of solvates. Under these facts, a general motivation to prepare other selective PKC inhibitor compounds (i.e., derivatives of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole rather than new forms thereof) is insufficient.

Fourth, no rationale is presented as to how one of ordinary skill would predict and prepare the particular crystalline form of the mono-hydrochloride form of the compound by Appellants as is required by the third prong of the *In re Cofer* test. In fact, the first procedure for preparing the claimed crystalline material was described in the present specification. (specification p. 14, lines 1-33) The rationale of *In re Heoksema* is applicable here:

> "If the prior art of record fails to disclose or render obvious a method of making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compound overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds."

(399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968))

Fifth, in addition to ignoring the test of *In re Cofer*, the Examiner fails to take into account the unpredictability of the crystallization art, such that the structure of any allegedly obvious new form, or its associated properties, cannot be determined by theory. Acid-base reactions (i.e., to form acid addition salts) are predictable in solution based on the relative pKas of the reactants. However, the resulting salts are generally amorphous, and there is no reliable predictor of crystallization.

Based on the foregoing arguments, claims 2 and 15 cannot be *prima facie* obvious over TEICHER, so that comparative data for rebuttal cannot be required.

In view of the foregoing arguments, Appellants respectfully assert that the final rejection of Claims 2 and 15 under 35 U.S.C. §103(a) as being obvious over HEATH was improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

SUMMARY

For all of the foregoing reasons, Appellants submit that Examiner's rejection of Claims 2 and 15, under 35 U.S.C. §102(b), 35 U.S.C. §102(e), and 35 U.S.C. §103(a) was in error and should be reversed. Appellants respectfully request reversal of the present rejection and passage of the present case to issuance.

Respectfully submitted,

/John A. Cleveland, Jr., Ph.D./
John A. Cleveland, Jr., Ph.D.
Attorney for Applicants
Registration No. 50,697
Phone: 317-276-0307

Eli Lilly and Company
Patent Division/JAC
Lilly Corporate Center
Indianapolis, Indiana 46285

CLAIMS APPENDIX

Claim 1 (cancelled).

Claim 2 (previously presented) Crystalline 2,5-dione-3-(1- methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole mono-hydrochloride having an X-ray diffraction pattern which comprises the following peaks: 6.8 ± 0.1, 10.9 ± 0.1, 14.2 ± 0.1 and $16.6 \pm 0.1°$ in 2θ; when the pattern is obtained from a copper radiation source (CuKα; $\lambda = 1.54056$ Å).

Claims 3-14 (cancelled).

Claim 15 (previously presented) A pharmaceutical composition comprising a salt of claim 2 and a pharmaceutical carrier.

Claim 16-22 (cancelled).

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None